

Special Contribution

## Report on the 1st Japan-Korea Workshop on Acupuncture and EBM -Proposal of Clinical Trials for the Future Japan-Korea Collaboration-

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### Abstract

The first Japan-Korea workshop on acupuncture and EBM was held on June 4, 2004 at Chiba in the 53rd annual scientific meeting of the JSAM. The purpose of this workshop was to exchange the experiences of clinical researches on acupuncture and moxibustion therapies, and to find out the issues and their solutions for developing the excellent clinical research to establish strong evidence. The final purpose was to develop a protocol for the collaborative work between both countries.

Drs. Kawakita (JSAM) and Jang (KAMS) chaired the workshop. Three speakers from Japan (Drs Takahashi, Nabeta, and Tsukayama) and three Korean speakers (Drs Seo, Lee and Moon) presented their data on the clinical researches of acupuncture, moxibustion and bee-venom injection. After their paper presentations, various issues were discussed on their research methodology for establishing more strong evidence of acupuncture. We got interesting new findings and understood various issues for conducting clinical researches especially RCT.

Although we could not develop a protocol for the collaborative research in this workshop, it was very fruitful workshop as the first step for the future Japan-Korea collaborative clinical study. The most important product of this workshop was we could understand each other and we confirmed the necessity of the future collaborative clinical research on acupuncture.

**Key words:** *Japan-Korea Workshop, EBM (evidence-based medicine), acupuncture and moxibustion, electro-acupuncture, RCT (randomized controlled trial), sham acupuncture, bee venom injection, protocol*

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### I. Background of this workshop

Japan and the Republic of Korea have gradually developed their own legislative and educational systems on acupuncture and moxibustion. Little information, however, has been exchanged between two countries. Rapid increase of information and personnel exchange in various fields between two countries, after World Cup Game

in 2002, in particular, has promoted the information exchanges in the field of acupuncture and moxibustion. Formal letter from Dr. Won-Chul Lee, then President of Korean Oriental Medical Society (KOMS) was sent to Dr. Shohachi Tanzawa, then President of Japan Society of Acupuncture and Moxibustion (JSAM) in June 2002. Since then several activities were conducted between two countries<sup>1)</sup>. On 6 June 2003, Preparatory Meeting of

"Japan-Korea Workshop on Acupuncture and EBM" was held in conjunction with 52 nd Annual Conference of JSAM at Takamatsu. Simultaneously, to encourage joint activities, a memorandum of understanding (MOU) among JSAM, the Korean Acupuncture and Moxibustion Society (KAMS) and KOMS was developed and formally signed on 14 February 2004 at Seoul<sup>2)</sup>. Based on such numerous efforts of the JSAM, KAMS and KOMS members, the first Japan-Korea workshop on acupuncture and EBM was held at Chiba on 11 June 2004.

## II. Purpose of this workshop

As the first step of the Japan-Korea collaboration of clinical trials in the future, this workshop was planned firstly to exchange the experiences of clinical researches on acupuncture and moxibustion therapies, and secondly to find out the issues and their solutions for developing an excellent clinical research for the strong evidence. The final purpose was to develop a protocol for the collaborative work but it might be premature to discuss at this stage, however these three purposes were scheduled then the workshop was started

Table 1. List of speakers and titles of their presentations

Speaker	Organization	Title of Paper
1 Takahashi N	JSAM	Results obtained from multi-center RCTs on the common cold and issues to be solved.
2 Seo J-C	KAMS	Is it possible to apply placebo auricular acupuncture to Korean? -The effect of placebo auricular acupuncture through single-blind method and randomized controlled trial
3 Nabeta T	JSAM	Results obtained from RCT of acupuncture on the shoulder stiffness and issues to be solved.
4 Lee S-H	KAMS	Randomized controlled double blind study of bee-venom therapy on rheumatoid arthritis
5 Tsukayama H	JSAM	An experience in conducting multi-center RCT of electro-acupuncture on the low back pain and issues to be solved.
6 Moon S-K	KOMS	Antispastic effect of electro-acupuncture and moxibustion in stroke patients

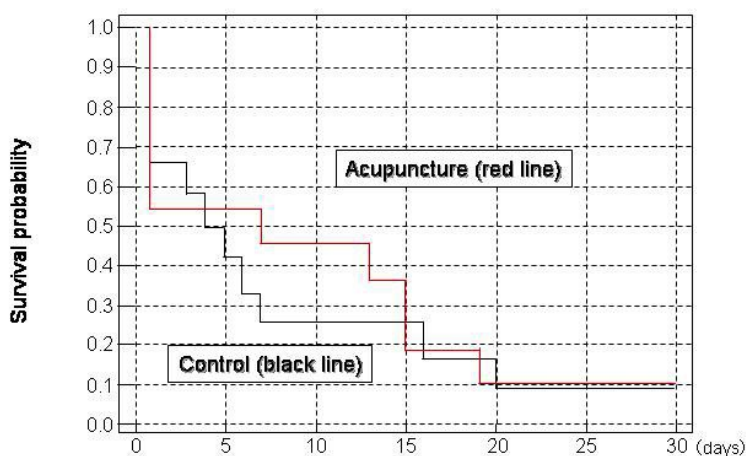


Figure 1. Survival analysis of the results of acupuncture on the CCD data. Kaplan Meier test was done. CCD (common cold diary; digital data was available, yes or no).

Table 2. Summary of the results of GLM analysis

center	CCD					CCQ	
	Cox (preventive)	Cox (curative)	GLM ( whole period)	GLM ( treatment period)	GLM ( sex)	GLM (whole period)	note
A	n.s.	n.s.	P=0.198 Sex*day: P=0.022	P=0.053 inversion	m>f	P=0.035	ACP<cont
B	P=0.0705	P=0.0097	P=0.001 sex: P=0.021	P=0.010	m>f	P<0.001	ACP>cont
C	n.s.	P=0.0059	P=0.360	P=0.071	m>f	P=0.029	ACP>cont
D	n.s.	n.s.	P=0.945	P=0.907 Sex*day: P=0.007	m>f	P=0.643	n.s.
E	n.s.	n.s.	P=0.644 Sex*day: P=0.000		m>f	P=0.218	n.s.

### III. The contents of workshop: presentation of papers from Japan and Korea.

The first Japan-Korea workshop on acupuncture and EBM was held at Chiba conference hall on 11 June, 2004. Over 20 members of the KAMS and KOMS also joined to the workshop. For convenience of the Japanese members of JSAM and students of acupuncture schools, slides for the presentation were prepared in English and Japanese. They were simultaneously presented on the screen. List of speakers and titles are summarized in Table 1.

#### *Topics of the 1st paper and raised issues*

Dr. Takahashi reported summary of a series of RCTs conducted by the EBM working-group of the research department of JSAM. The purpose of this study was to evaluate the effectiveness of acupuncture on the common cold symptoms. The main outcome measure was the symptoms of common cold questionnaire. Intervention was manual needling to the throat with de-chi. Non-treatment group was set as the control.

Figure 1 shows the effect of acupuncture on common cold dialy (CCD) by Kaplan- Meier analysis, and more survivals exist in the acupuncture group during treatment period (14 days). Table 2 shows the summary of results of acupuncture manipulation on the common cold questionnaire (CCQ). A significant acupuncture effects on CCQ was obtained by GLM (general linear model)

analysis, however there were also significant inter-center and sex differences.

The results of multi-center RCT of the indirect moxibustion to the neck or subcutaneous needling as more regulated interventions than the needle manipulation. The results did not clearly show the effectiveness of these interventions.

Several issues were pointed out. The subjects were the students of the acupuncture schools, and the control group was no-treatment. A significant inter-center difference of effectiveness was also apparent.

Based on these experiences of the multi-center RCT, application of n-of-1 trials on the acupuncture research was proposed as a useful individualized experimental design.

It is worth considering for the future experimental design for the patient-oriented and order-made acupuncture therapy (see ref 9).

#### *Topics of the 2nd paper and raised issues solved.*

Dr. Seo reported on the issue on the placebo intervention for the acupuncture RCT. The placebo needle he developed was a blunt tip with short length, which could not be penetrated into the skin.

The random allocation was well planned and performed, and the sensations elicited by auricular needling by the real and placebo needle were similar. The warmth, fullness, pain, activity and radiating sensations were provoked, however the incidence was less in the placebo

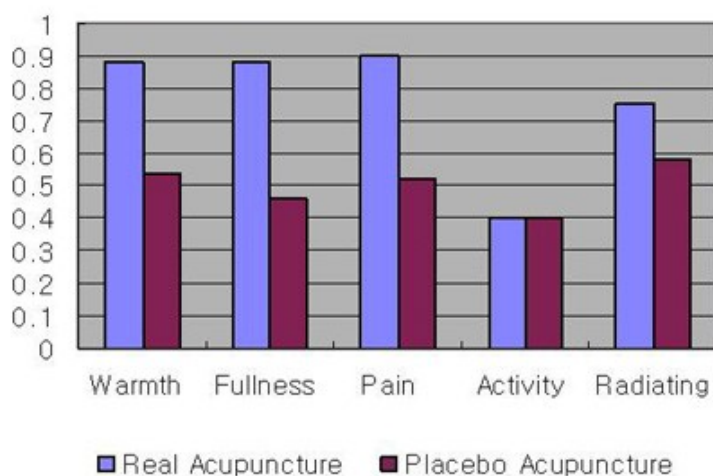


Figure 2. Comparison of acupuncture sensations elicited by real and placebo needle.

Table 3. Ability to differentiate real and placebo acupuncture

	Real acupuncture	Placebo acupuncture	Total
Thinking it as the real	26	10	36
Thinking it as the placebo	10	26	36
uncertain	12	12	24
Total	48	48	96

(P=0.0008, chi-square test)

Table 4. Ability to differentiate real and placebo acupuncture for naive and experienced acupuncture recipients

	Correct	Incorrect	Uncertain	Total
Naive	9	6	8	23
Experienced	17	4	4	25
Total	26	10	12	48

(P=0.128, chi-square test)

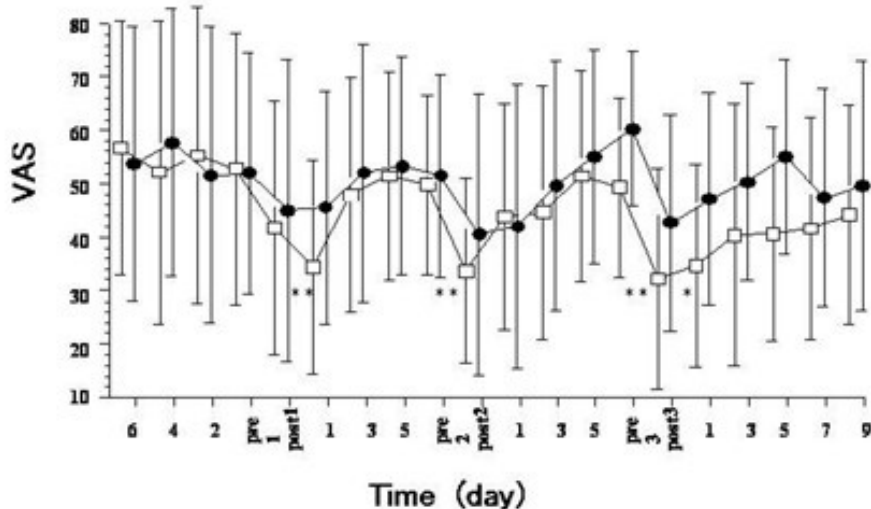


Figure 3. Suppression of VAS of the neck and shoulder pain by repetitive acupuncture treatment in volunteers.  
VAS: visual analogue scale

Table 5. Assessment of blinding answers to the question "How did you feel when the acupuncture needle was inserted?" in acupuncture (AG) and sham (SG) groups.

	Inserted to muscle	not penetrated skin	Could not discriminate
AG	11	4	2
SG	9	6	2

No significant difference between AG and SG was found (chi-square=0.6, P=0.74)

group (Figure 2). Discrimination of real and placebo needle was statistically significant, that is, placebo needle did not work well (Table 3).

On the other hand, he suggested that the experiences of acupuncture therapy affect on the discrimination of the real and placebo. Table 4 shows that the experienced group detected the real one more accurately than those of acupuncture-naïve patients, although the difference was not significant.

Based on the literatures of placebo research in the foreign countries, he also pointed out a possibility of the racial difference. These results were important to select the placebo intervention and subjects in acupuncture research. Expression of the placebo needle was a matter

of discussion as sham intervention has been more common term as the true placebo acupuncture is impossible theoretically.

#### *Topics of the 3rd paper and raised issues solved.*

Dr. Nabeta reported the RCT conducted on the student volunteers who have complaint of pain and stiffness in the neck and shoulder. Repetitive application of manual acupuncture, inserted to the muscle and sparrow pecking technique used, to the tender points of neck and back once in a week for 3 weeks produced cumulative effects as shown in Figure 3. In the previous trials, the

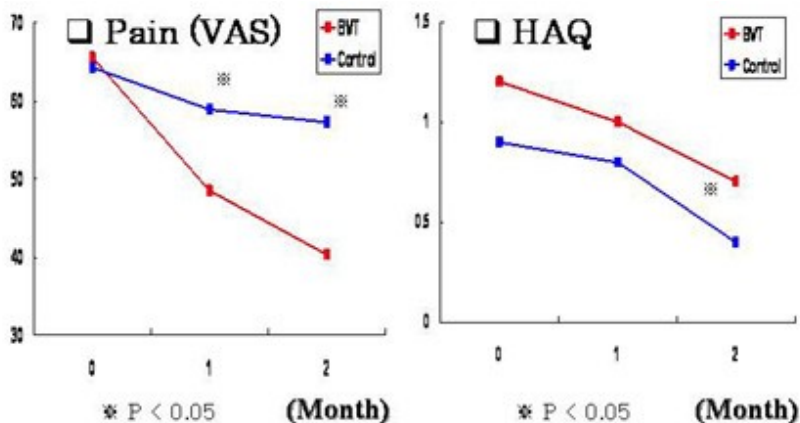


Figure 4. Effects of bee venom injection on pain and HAQ of the arthritis patients  
HAQ: health assessment questionnaire

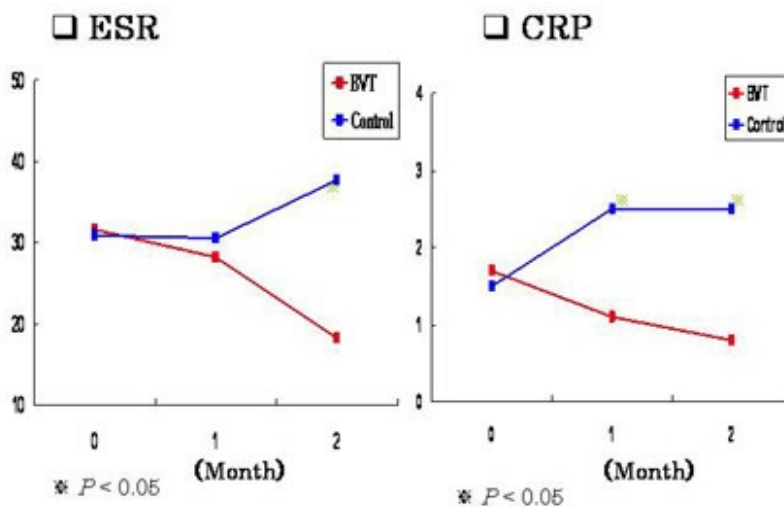


Figure 5. Effects of bee venom injection on ESR and CRP of the arthritis patients  
ESR: erythrocyte sedimentation rate CRP: C-reactive protein.

minimum acupuncture was shown to be inadequate as control intervention as it actually worked. Then unique sham acupuncture was considered and statistically significant effects were detected compared with the baseline but not between the groups.

The procedure of gesture of needling was successfully blinded as shown in Table 5, however it was pointed out that these sham procedure was applicable only on the back where the subjects could not see. The subjects of this RCT were student volunteers in Japanese

acupuncture school and they were familiar with acupuncture sensations, so the success of masking by the present sham procedure is meaningful. However, the volunteer bias was an important factor, so the results should be analyzed and discussed carefully. Importance of the selection of adequate stimulating points (tender point) was also stressed.

*Topics of the 4 th paper and raised issues solved.*

Dr. Lee reported a clear effect of BVI (bee venom injection) on the patients of rheumatoid arthritis. BVI was applied to the acupuncture points nearby the major joints (twice a week for 8 weeks), and control intervention was saline injection to the same points. Random allocation was sufficiently done, and the results clearly indicated that the BVI improved the tender joint count, swollen joint count, morning stiffness, pain (VAS), HAQ, ESR and CRP. The effects of BVI on VAS and HAQ were shown in Figure 4. Those of ESR and CRP values in

laboratory examinations were summarized in Figure 5. The effects increased with time of treatments, so it was very interesting to know the after-effects of the BVI.

The procedure was shown to be very useful for the arthritis patients, however, it is not applicable in Japan. Japanese acupuncturists are not allowed to use the drug injection for their treatment. This was a big difference in the acupuncture related medical system between Japanese and Korea.

Table 6. Requirement for conducting multi-center trial

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- Clear concepts which are really accepted and shared by all of the working group member are needed in acupuncture multi-center trial.
    - Top-down model need powerful leadership, clear strategy and incentive for researchers.
    - Training of clinical trial is needed.
    - Spontaneous commitment to study group is desirable.
  - Conducting RCT need a lot of cost.
    - Financial support is needed to conduct multi-center RCT in multi-disciplinary collaboration
  - Multidisciplinary collaboration is recommended
    - Clinical trial expert
    - Clinical medicine expert
    - Bio-statistics expert
    - Acupuncture researcher
  - Clear definition of the role and responsibility of each working group member were needed in multi-center trial
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Table 7. Requirement for conducting multi-center trial

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- Concept of quality control is useful in multi-center trial
    - Monitoring for allocation, research setting and implementation process in each institutions (monitor)
    - Trial coordination in each institution (coordinator)
    - Data management (data manager)
    - Concealed allocation (independent controller)
  - Requirement in trial design
    - Appropriate acupuncture procedure should be based on
      - Pre-existing evidence
      - Review of standard texts
      - Research of usual practice in reality
    - Outcome measurements should be validated in each language
  - Difficulty of patient recruitment from outpatient of acupuncture clinic has not been solved in Japan.
    - Collaborations with conventional medical system
    - Advertising of patients recruitment
  - Consideration for the ethical issue
    - An approval from ethical committee

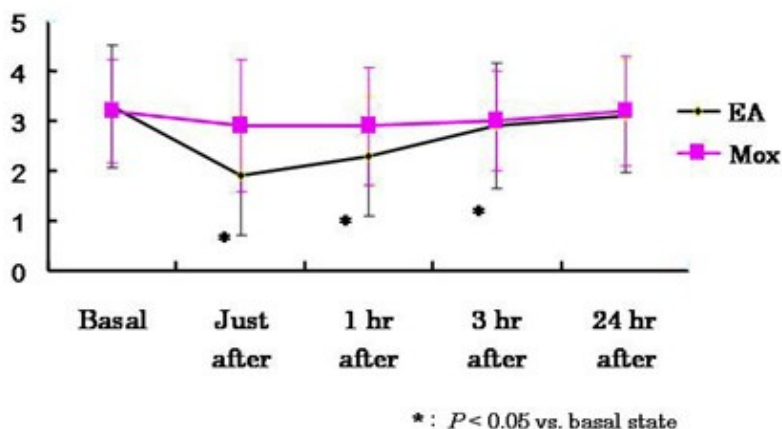


Figure 6. Changes of MAS after the first treatments

MAS: modified Ashworth scale

EA: additive specific electro-acupuncture to specific points for spasticity.

Mox: additive moxibustion to specific points for spasticity.

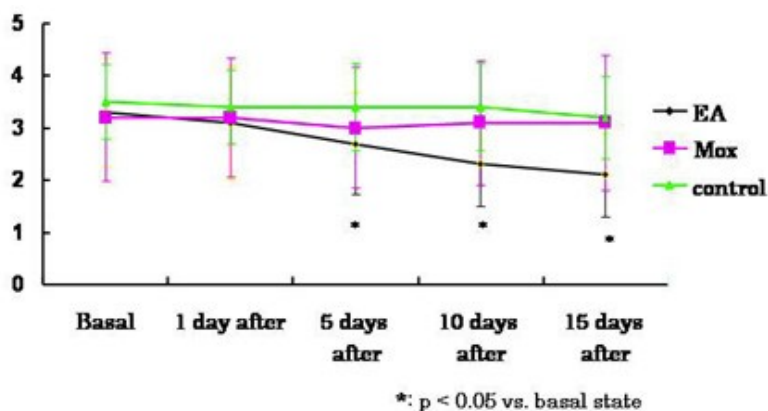


Figure 7. Changes of MAS according to treatment period

See Fig. 6 for abbreviations

Table 8. Issues to be solved for the future collaboration of Japan-Korea clinical research

1. Validity of RCT for Future Study
2. Methods of Random Allocation
3. Selection of Control Intervention
4. Necessity of Placebo or Sham Interventions
5. Selection of Outcome ( Subjective, Objective)
6. Calculation of Sample Size
7. Like-hood of Multi-Center RCT in Japan and Korea
8. Difference of Medical System between Japan and Korea
9. Choice of Target Disease for the Future Study
10. Financial Support



*Topics of the 5 th paper and raised issues solved.*

Dr. Tsukayama introduced conducting process of the first multi-center randomized controlled trial (RCT) of acupuncture for lumbago in Japan supported by "Foundation for Training and Licensure Examination In Anma-Massage-Acupressure, Acupuncture and Moxibustion" The studies were planned as a model case of multi-center acupuncture RCT in Japan by the Foundation and were performed at clinical facilities in 4 universities or colleges in Japan from 1995 until 1999. The studies consisted of two trials. The trial I (1995-1996) failed to conduct uniform multi-center RCT. The protocol was implemented into different procedure by each institution and the number of subject recruited did not reach the target.

In the trial II (1996-1999), the Foundation asked the trial expert to lead the study process. The concept of quality management on RCT was introduced into the trial II, and the role and responsibility of each working group member had been clearly defined. These attempts led the trial successfully and a uniform multi-center RCT was able to be conducted among institutions. Electroacupuncture was examined and control intervention chosen was real TENS in the trial II. Both interventions were applied twice a week for 2 weeks (4 treatments). Subjective pain intensity tended to decrease with time by both interventions, and no difference was detected between the groups. Based on the experiences of multi-center RCT on lumbago, he proposed several issues for the future clinical research (Table 6,7)

The clear concepts in management and specific purpose of RCT are required and those should be well-understood by all the members participated in the project. Regarding the intervention, appropriate acupuncture procedure should be chosen based on the pre-existing evidence, review of standard textbooks and usual practical reality. Patient recruitment and setting of the entry criteria, resolution of ethical issues and financial support are also important. These issues were pragmatically very important for the future collaborative activities of acupuncture research.

*Topics of the 6 th paper and raised issues solved.*

The last speaker was Dr. Moon. He showed clear results of anti-spastic effect of acupuncture on the stroke patients. He compared the effects of additive EA, addi-

tive moxibustion for the spasticity and routine acupuncture treatment for the stroke. Routine acupuncture was used as the control intervention. Both specific treatments were done every two days (8 times during 15 days). Results were very clear. Immediately after the EA the MAS (modified Ashworth scale) value was improved only in the additive EA group significantly (Figure 6), and the effect of additive EA group continued and the best improvement was obtained at the end of treatment session (Figure 7).

The control setting is very important issue of design of a protocol. In his study, the routine acupuncture treatment was chosen as the control intervention, and it actually worked as control intervention (no-effect produced). It is very reasonable control intervention for the patients' benefit in the clinical trials. Comparison of routine treatment and the additive specific acupuncture therapy may be good choice in the future clinical trials.

#### **IV. General discussion**

In Table 8, ten items were listed for the general discussion. During the presentation of papers, some items were referred by the speakers and discussed among the participants.

Regarding the research design, all presenters employed the RCT as the best design for obtaining strong evidence. On the other hand, Dr. Takahashi pointed out the necessity of n-of-1 clinical trial as individualized intervention is essentially important for acupuncture research. In the multi-center RCT on the common cold, he found a significant inter-center difference. A uniformed intervention in each center was keenly required, however it was technically quite difficult to standardize the acupuncture manipulation for obtaining similar acupuncture sensation in each subject.

The necessity of random allocation of subjects in RCT was agreed by all participants and it was conducted in the papers presented, however the importance of the group-comparison analysis should be reminded.

Regarding the control intervention, non-treatment control, sham/placebo needling, TENS were used in the presentations. In general, importance of sham intervention in acupuncture RCT was agreed, however the methodological difficulties of placebo control in acupuncture were also stressed among the researchers. Then non-treatment control was set as the student subjects were familiar with the acupuncture sensation and easily dis-

criminate the real and sham acupuncture in Japanese acupuncture school. Dr. Nabeta succeeded to develop sham acupuncture, but it had limitation that it was applicable only to the back. On the other hand, Dr. Seo examined the efficacy of placebo auricular needling and pointed out a possibility of racial difference among United Kingdom and Korea. It was an important issue that in both Japan and Korea true acupuncture naive subjects were rare so the sham acupuncture seems to be more difficult in Asian countries than Western countries. Comparison of routine acupuncture and additive specific acupuncture treatment used by Dr. Moon and its clear success was also important from the view points of patient's benefit in RCT. It was also pragmatically useful for the future trials.

Sample size calculation was done in relatively large scale RCTs in Japan. Its importance for excluding so-called type II error in to conclude the results obtained. In the future collaborative clinical study it will be important so a preceding pilot study will be required. To conduct a multi-center RCT in Japan and Korea, it is very important to discuss on the target disease and financial support as pointed by Dr. Tsukayama.

Because of the shortage of time, we could not discuss on the issues listed in Table 2 sufficiently at the workshop, however, we could understand the different situation of Japanese and Korean acupuncturists, and the difficulties for conducting the multi-center RCT. Bee venom injection reported by Dr. Lee was a very attractive, however the Japanese acupuncturists can not use it for the legal regulation. We knew the situation of each country and could exchange various information about the clinical research conducted in both countries.

So we wish to conclude that the first Japan-Korea workshop on acupuncture and EBM was fruitful and meaningful as the first step of the future collaborative clinical research between two countries.

## V. Future issues of the workshop

We could not make up a draft of protocol for the collaborative clinical research, however the participants might agree that it was the meaningful first step for it. We still have many issues to be discussed and resolved. After the workshop, several issues for the next workshop were discussed, and we agreed to have small meeting before the next Korea-Japan Workshop on Acupuncture and EBM held at Korea in October, 2005.

A regular video conference among the countries was planned firstly, however it is still under consideration because of its technical difficulty and cost. Now we are planning a small meeting in this fall in Korea to promote the discussion for the further progress.

To clarify the purpose of the collaborative study will be the most important issue.

To make strong evidence of acupuncture brought by RCT is undoubtedly important, therefore we need to decide an adequate target disease for the clinical research. Recently numerous clinical researches of acupuncture have published in western countries, and we need to find unique or specific target for the clinical research for the purpose of strengthening our originality in research. If we want to stress the importance of technical matters of acupuncture and moxibustion developed in Korea and Japan, we should consider the use of n-of-1 trial design or other research designs instead of the commonly standardized RCT.

We sincerely hope the participants and readers of this report send us their frank opinions for the next Korea-Japan Workshop to our mail addresses.

## VI. Acknowledgements

We sincerely thank to the organizing committee of Chiba Meeting for setting this workshop, and to Dr. Tsutani, Director of International Affair of JSAM, and Dr. Tanzawa, President of JSAM, for their arrangement since last year, and to the members of KAMS and KOMS to collaborate this workshop.

A part of the clinical trials conducted in Japan were supported by the AHAKI foundation (Foundation for Training and Licensure Examination in Anma-Massage-Acupressure, Acupuncture and Moxibustion)

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## Appendix

All six speakers kindly agreed to exhibit their slides to the members of the JSAM, KAMS and KOMS for promoting the clinical research in both countries. It is allowed for the personal use only, so please do not use for other purposes. You can see these slides at the homepages of the JSAM, KAMS and KOMS soon.